



Properties of an In Vivo Fractured Poly(Methyl Methacrylate) Cranioplasty After 15 Years

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■ **BACKGROUND:** In 2001, a 27-year-old man was diagnosed with a meningioma with skull bone involvement. A craniectomy was performed and a CMW-3 poly(methyl methacrylate) cranioplasty was manually manufactured to reconstruct the remaining cranial defect. In 2016, he complained about progressive neurologic impairment. A computed tomography scan revealed that the cranioplasty had fractured into 4 dislocated pieces. Removal was indicated, and during the same operation a polyetheretherketone patient-specific implant was inserted.

■ **METHODS:** The fractured cranioplasty was compared with freshly prepared CMW-3 specimens to determine whether the material properties had changed during 15 years in vivo. Gel permeation chromatography, micro-computed tomography, and flexural strength tests were performed. The fracture itself was analyzed using finite element analysis.

■ **RESULTS:** The polydispersity index and molecular weight were not significantly different for the fractured cranioplasty and CMW-3. The fractured cranioplasty contained a total porosity of 10.7%, fresh CMW-3 cured at atmospheric pressure contained 4.1%, and 0.06% when cured at 2.2 bar. The flexural strength of the CMW-3 cured at 2.2 bar was significantly higher than both the fractured cranioplasty and CMW-3 cured at atmospheric pressure. Finite

element analysis showed stress of 12.2 MPa under a load of 100 N on a weak spot.

■ **CONCLUSIONS:** This ex vivo study shows that CMW-3 after 15 years in vivo was not influenced in molecular weight or flexural strength. However, the design of the implant and the handling of the poly(methyl methacrylate) seem to be important factors to improve mechanical properties of cranial reconstructions.

INTRODUCTION

After decompressive craniectomy, a cranioplasty is recommended to protect the brain, improve esthetics, and increase psychosocial well-being.¹⁻⁵ Most documented materials for cranioplasty are autologous bone, titanium, poly(methyl methacrylate) (PMMA), hydroxyapatite, and polyetheretherketone (PEEK), each with their own benefits. However, there is still no consensus on the optimal material for cranial reconstructions.^{6,7}

One of the most frequently used alloplastic materials is PMMA, which was developed in 1901 by Dr. Otto Röhm and was adopted early in aeronautical engineering.⁸ After several years, PMMA was introduced in the clinic and was gradually applied for dental applications, hip and knee arthroplasties, and cranial reconstructions.⁸⁻¹²

Especially in cranial reconstruction, material handling has undergone a transformation in the last decade. Traditionally, PMMA powder

Key words

- Acrylic
- Decompressive craniectomy
- Fracture
- Implant
- Skull

Abbreviations and Acronyms

- 3D:** 3-Dimensional
FEA: Finite element analysis
GPC: Gel permeation chromatography
PDI: Polydispersity index
PEEK: Polyetheretherketone
PMMA: Poly(methyl methacrylate)
PSI: Patient-specific implant

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and methyl methacrylate liquid are hand-mixed and cured directly in the cranial defect.^{9,12} An important disadvantage of this procedure is the high temperatures reached during curing, which could inadvertently be transferred to the bone, dura, and brain. Nowadays, a 3-dimensional (3D) mold of the cranial defect can be manufactured to produce patient-specific implants (PSIs). Subsequently, PMMA is pressed into a mold and cured. After cooling down, minor adjustments can be made to the implant, after which it is placed into the cranial defect.¹³⁻¹⁶ There is extensive literature available on the behavior of PMMA; however, controversy exists, especially toward toxicity.¹⁷ An important remaining question is whether the material behavior of PMMA changes over time in non-load-bearing locations in the human body, such as the calvarium.

Advances in medical technology, such as patient-specific allogenic reconstruction, have led to an improvement of patient outcomes.¹⁸ Therefore, it is important to understand *in vivo* material behavior over time. It is also important to understand why implants fail, so the design and material may be further improved on.

In this study, a 15-year-old *ex vivo* cranioplasty was retrieved. The chemical, structural, and mechanical properties of this fractured cranioplasty were evaluated to investigate changes of these properties in the human cranium and to find the origin of the failure.

MATERIALS AND METHODS

Case

In 2001, a 27-year-old man, with diabetes mellitus type II, visited the department of neurosurgery with complaints of sensory disturbances in the right side of his body, character changes, diminished vision, and dysphasia. Magnetic resonance imaging was performed, and the patient was provisionally diagnosed with a bilateral parieto-occipital meningioma with reactive changes of

the cranial bone (Figure 1). A total resection was indicated, and a direct reconstruction of the cranial defect was planned.

A bicoronal incision was performed, a skin flap was detached, and the involved bone was surgically visualized and removed. The resulting defect had a circumference of 400 mm. After tumor resection and closure of the dura, a PMMA cranioplasty was prepared according to the manufacturer's instructions using CMW-3 (DePuy International Ltd., Leeds, United Kingdom). The malleable PMMA was put into the defect for the correct size and molding, after the dura was protected with damp gauzes. After hardening, small adjustments were made with a burr to create a perfect fit. After this, the cranioplasty was fixed with sutures. After closure of the skull defect, a subcutaneous wound drain was placed. The total operation time was approximately 14 hours with 4.5 L blood loss. The pathologic diagnosis was as expected: meningotheliomatous (syncytial) meningioma (World Health Organization grade I) with ingrowth into the cranial bone.

In the years after the initial cranioplasty, the patient had multiple epileptic seizures; with the use of lamotrigine these did not recur. The patient lived by himself, was eventually permitted to drive a car, and did not have any complaints. In 2016, 15 years after the initial cranioplasty, he complained about progressive headaches, memory impairment, poor vision, inability to operate motor vehicles, and unstable gait. The patient could not recall any trauma involving the cranioplasty. On physical examination, the cranioplasty was palpable and seemed loose. A computed tomography scan with 3D reconstruction revealed that the cranioplasty had fractured into 4 pieces, which were dislocated (Figure 2, left).

Removal of the fractured PMMA cranioplasty was indicated, and during the same operation a PEEK PSI was inserted (Figure 2, middle and right). The shards of the fractured implant were sealed in separate plastic bags and stored at 4°C in the dark.

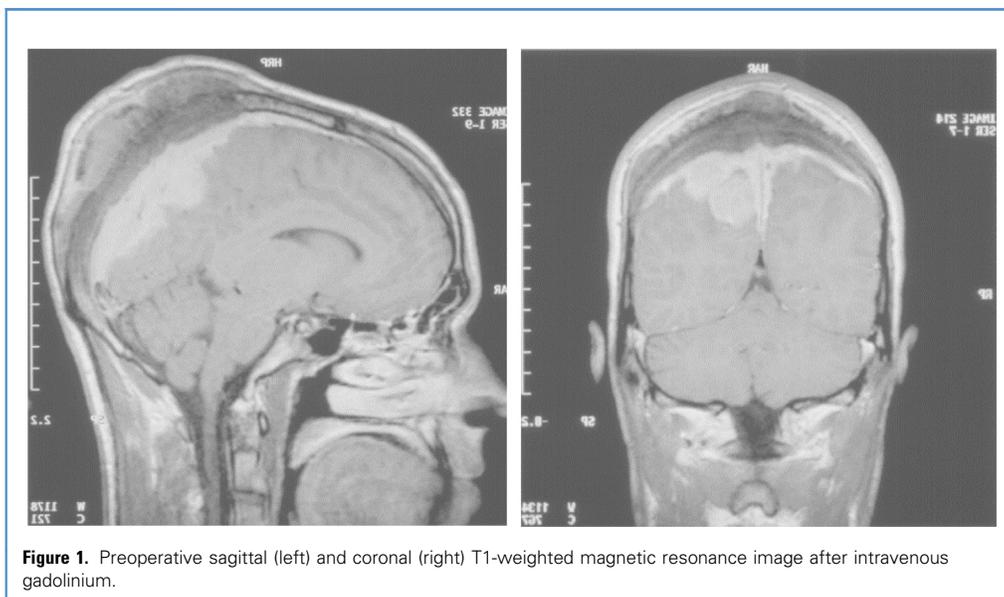


Figure 1. Preoperative sagittal (left) and coronal (right) T1-weighted magnetic resonance image after intravenous gadolinium.

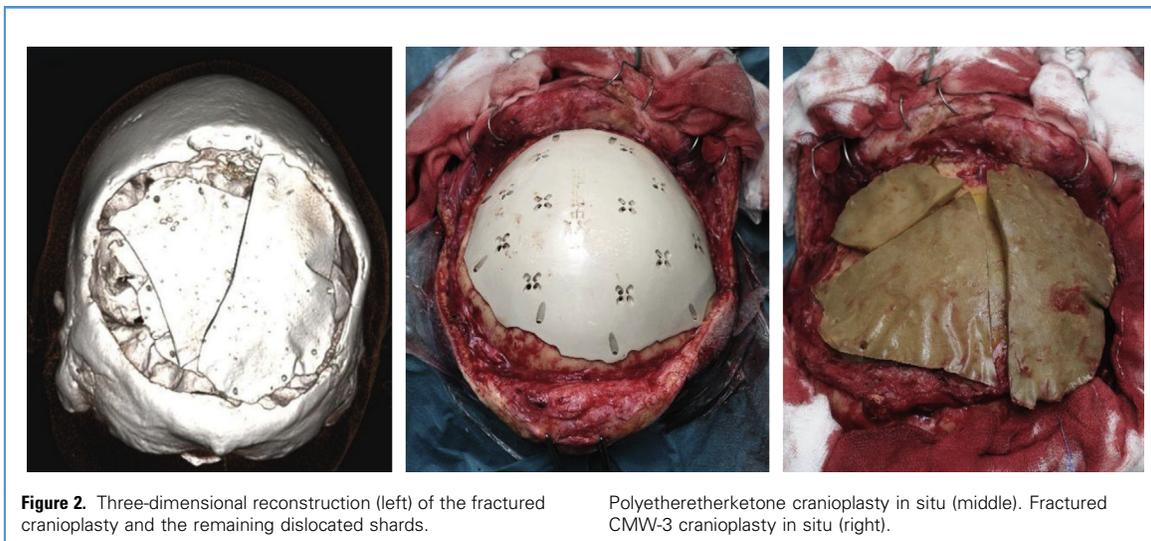


Figure 2. Three-dimensional reconstruction (left) of the fractured cranioplasty and the remaining dislocated shards.

Polyetheretherketone cranioplasty in situ (middle). Fractured CMW-3 cranioplasty in situ (right).

The PSI operation was complicated by a postoperative epidural hematoma, which was surgically evacuated. After 2 months, the patient visited the outpatient clinic and reported an improvement of his symptoms.

Three analytical techniques, gel permeation chromatography (GPC), microcomputed tomography, and flexural strength, were used to determine whether the chemical, structural, and mechanical properties of CMW-3 had changed during 15 years in vivo. With the use of finite element analysis (FEA), the mechanical behavior of the fractured implant was analyzed to better understand the underlying reasons for failure.

Specimen Preparation

The fractured cranioplasty was compared with fresh specimens of CMW-3 (PMMA). Following the manufacturer's instructions, the PMMA particles (40.0 g) were mixed with MMA liquid (17.9 g) in a vacuum holder. The malleable CMW-3 was put into a nylon 3D printed cranial mold. One specimen was cured for 30 minutes at atmospheric pressure, and another was cured for 30 minutes at a pressure of 2.2 bar.

GPC

The average molecular weights and their distributions were assessed by GPC. Four small samples were collected from the edge of the fractured implant. To compare, 2 fresh samples of CMW-3 were retrieved. In total, 6 samples were analyzed using GPC to determine the relative molecular weights. The samples of the fractured implant were washed with demi water to remove as many blood stains as possible, and all samples were measured in duplo.

Suspensions were formed by mixing each sample in tetrahydrofuran while stirring and heating, resulting in sample concentrations of around 2 mg/mL. These suspensions were filtered to remove the present insoluble salts and additives and injected into the GPC column (300 × 7.5 mm, 3- μ m particles, MIXED-C and MIXED-D columns connected in series [Polymer Labs,

currently Agilent Technologies, Santa Clara, California, USA]). The mobile phase consisted of tetrahydrofuran at 1 mL/min and 40°C. Ultraviolet/visible photodiode array and refractive index detectors were used to analyze the samples and were compared with polystyrene standards.

Porosity and Density

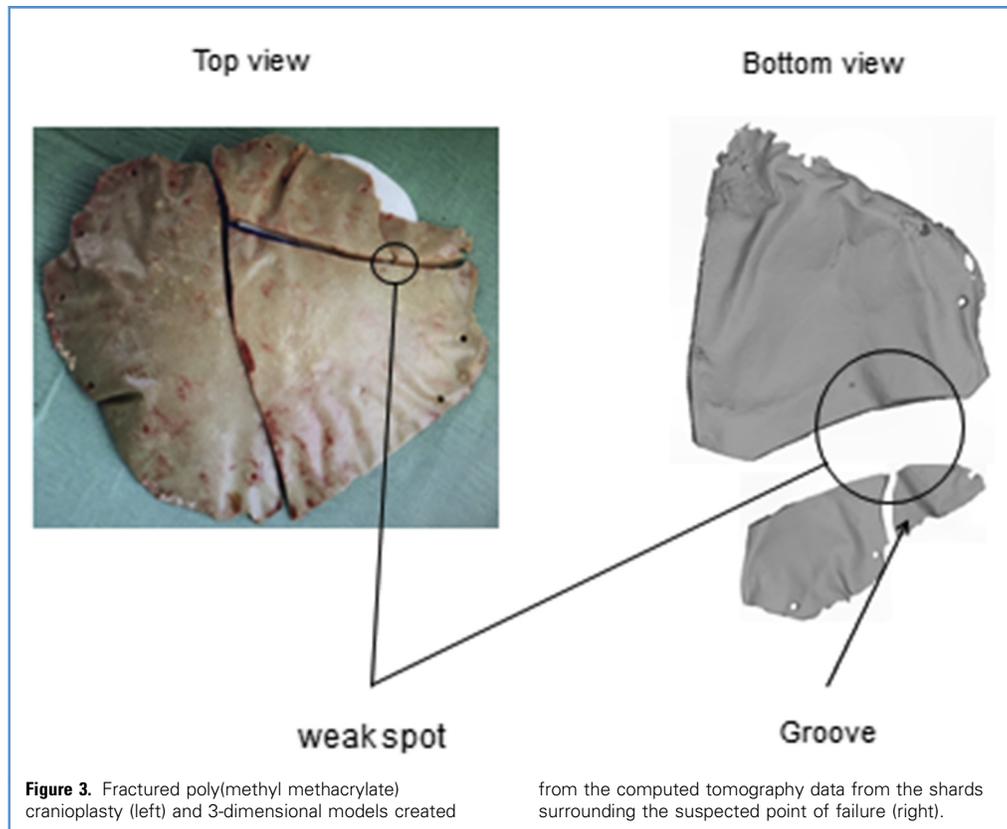
The porosity was determined by measuring the density and using 3D microcomputed tomography. The density of the specimens was measured using a Mettler Toledo AT261 (Greifensee, Switzerland) analytical balance. Microcomputed tomography data were acquired using a SKYSCAN 1272 (Bruker, Kontich, Belgium) with the following settings: voltage = 100 kV, current = 100 μ A, exposure time = 31.2 seconds, pixel size = 6.7 μ m, and 1200 projection angles. The porosity was determined with CTAn software (v1.7.17 [Bruker]).

Flexural Strength

The fractured implant and the CMW-3 specimens were sawed with a 0.3-mm-wide diamond saw (Ukam Industrial, Valencia, California, USA) into 10 × 10 × 13-mm rectangular specimens (10 per group) and wet grinded with standard metallographic grinding paper (P500, P1000, and P1200). The specimens from the fractured cranioplasty were harvested from the center of the implant. Before testing, the specimens were immersed in a water bath at 37.0°C ± 1.0°C for 50 ± 2 hours. The flexural strength was determined at 37.0°C ± 2.0°C, using a 3-point bending test with a crosshead speed of 1.0 mm/min and a distance between the supports of 10.0 mm. Each specimen was tested until fracture. The ultimate flexural strength (σ) was calculated using the following equation:

$$\sigma = \frac{3Fl}{2bh^2}$$

where F is the maximum load exerted (in newtons), l is the distance between the supports (in millimeters), b is the width, and h is the height of the specimen (in millimeters).



FEA

The fractured cranioplasty (Figure 3) was visually inspected, and a simplified 3D model was created to predict the stresses in the expected point of failure (Figure 4). More precisely, this point showed typical characteristics of an initial point of fracture, the so-called mirror-hackle zone,^{19,20} a groove originating near the edge of the implant, and an exposed pore located at the thinnest portion of this groove. Finite element modeling was carried out using FEMAP software (FEMAP 11.1.0 [Siemens PLM Software, Plano, Texas, USA]); the analyses were performed with Nastran software (NX Nastran [Siemens PLM Software]).

The implant and surrounding bone were modeled into a sphere-like shape with an outside diameter of 140 mm. The thickness of the implant model was chosen as 4.5 mm, the average thickness of the fractured implant. The dimensions of the groove and exposed pore in the broken implant were measured using digital dial calipers (Mitutoyo, Kawasaki, Japan). The models were composed of 17,345 parabolic tetrahedron solid elements. The implant was fixed to the patients' cranial bone during surgery and held into place by surrounding tissues thereafter; therefore, the interface between the implant and the surrounding bone was designed as fixed, allowing no movement in any direction. Material characteristics of the models were as follows: PMMA: Young's modulus = 2158 MPa (experimental result of the fractured cranioplasty), Poisson ratio = 0.38; bone: Young's modulus = 15 GPa, Poisson ratio = 0.3. Two analyses were performed using different loads at the outside of the implant and perpendicular to

the surface: one with a load of 100 N on the central node and one with a load of 100 N on the node opposite to the weak spot. The material properties used in the models are shown in Table 1.

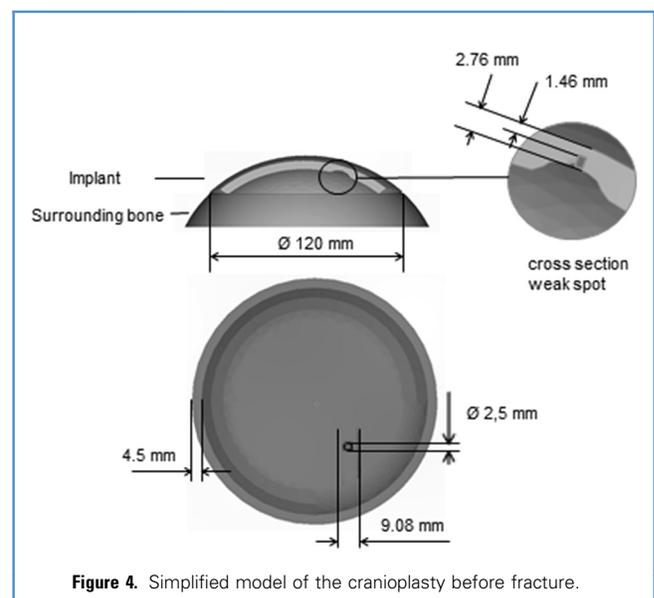


Table 1. Maximum Tensile Stress (σ) and Young's Modulus (E) of the Materials Used in the Models

Material	σ (MPa)	E (GPa)
Bone	-	10
Implant	70	2.2

The maximum tensile stress (solid maximum principle stress) and the displacements in the implant and surrounding bone layer were calculated. In postprocessing, the contour option, average elemental, without use of the corner data, was used to visualize the results.

The amount of absorbed energy in the implant under load was calculated as follows:

$$E = \frac{1}{2} Ff$$

where E is the absorbed energy (in joules), F is the applied load (in newtons), and f is the displacement in the direction of the applied load (in meters).

The absorbed energy on hitting a flat surface was calculated using the following:

$$E = \frac{1}{2} mv^2$$

where E is the absorbed energy (in joules), m is the mass (in kilograms), which was assumed to be 2.25 kg, half of the mass of the patient's head (4.5 kg²¹) as it is supported at one side, and v is the speed (in meters per second).

Using these equations, the corresponding speed was calculated at which an impact with a flat and hard surface would cause the maximum tensile stress required for fracture.

Statistical Analysis

The flexural strength data were statistically analyzed using 1-way analysis of variance followed by Tukey post hoc test ($\alpha = 0.05$) in SPSS version 24.0 (IBM, Armonk, New York, USA). Student t test was used to analyze the GPC data.

RESULTS

In this ex vivo study, a CMW-3 PMMA fractured cranioplasty, which was part of the patient's cranium for 15 years, was compared with fresh specimens of CMW-3 cured at 2.2 bar and at atmospheric pressure. To determine whether the chemical, structural, and mechanical properties of CMW-3 change over time, GPC, microcomputed tomography, and flexural strength tests were performed. The fracture itself was analyzed using FEA.

GPC

All samples were analyzed using refractive index detection because PMMA does not contain chromophores; the ultraviolet/visible photodiode array detector therefore, did not produce useful data (Figure 5). The number average molecular weight, weight average molecular weight, Z average molecular weight, and polydispersity index (PDI) were comparable for each group (Table 2). The PDI was not significantly different for the fractured implant and

CMW-3 ($P = 0.94$). No significant difference in number average molecular weight ($P = 0.76$), weight average molecular weight ($P = 0.70$), or Z average molecular weight ($P = 0.78$) was detected between the implanted material and CMW-3.

Porosity

The density of the fractured cranioplasty was 1.147 g/cm³, whereas the densities of CMW-3 were 1.156 (cured at atmospheric pressure) and 1.246 g/cm³ (cured at 2.2 bar). This results in a macroscopic porosity of 7.9% for the fractured cranioplasty and 7.3% for CMW-3 cured at atmospheric pressure. The microcomputed tomography of the fractured cranioplasty showed a total porosity of 10.7%. The specimen of the CMW-3 cured at atmospheric pressure had a porosity of 4.1%, and the specimen of CMW-3 cured at 2.2 bar had a porosity of 0.06% (Figure 6).

Flexural Strength

The results of the mechanical tests and statistical analysis are summarized in Table 3. The flexural strength of the fractured cranioplasty and CMW-3 cured at atmospheric pressure was not significantly different; however, the flexural strength of CMW-3 cured at 2.2 bar was significantly higher than both of the aforementioned groups.

FEA

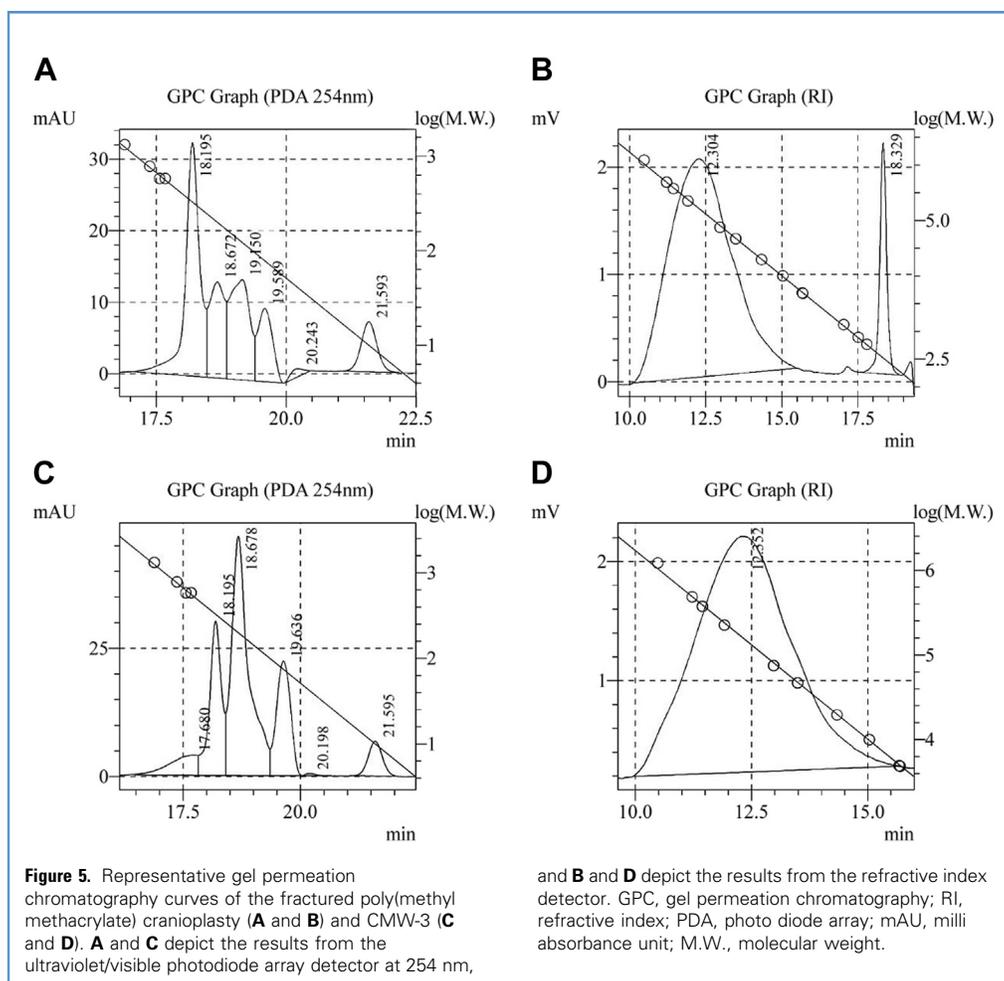
The maximum tensile stresses in the models under a load of 100 N in, respectively, the center and the weak spot in addition to the resulting translations are shown in Table 4 and Figure 7. The stress under the load of 100 N on the weak spot was 12.2 MPa. Because the material displays linear elastic behavior, a load of 503 N is needed to fracture the implant. This load corresponds with hitting a flat and hard surface at a speed of 0.42 m/s, which results in a similar fracture stress.

DISCUSSION

This ex vivo study reports the material properties of a fractured PMMA cranioplasty made of CMW-3, after being part of the human cranium for 15 years, and fresh specimens of CMW-3. The following trends were observed: 1) the chemical and mechanical properties of CMW-3 did not significantly change during the 15 years in vivo, 2) failure of the cranioplasty can be attributed to the heterogeneity in thickness and porosity, and 3) improvements in the mechanical properties of PMMA cranioplasties can be achieved by ensuring a consistent thickness of the cranioplasty and by curing the implant under increased pressure.

Failed cranioplasties are generally not subjected to further investigations beyond basic microbiologic evaluation in cases of infection. In our study, a single failed PMMA cranioplasty was analyzed and compared with fresh specimens of CMW-3. It is crucial to determine how the human body influences material properties of such implants over time, to ensure optimal clinical outcomes and possibly prevent further operations for the patient.

PMMA-based polymers have been used for many years in medical devices with their specific formulations and applications. It is used intraoperatively for fixation of artificial joints to bone, for dentures, and for cranial reconstructions.⁸⁻¹² The information on chemical and mechanical behavior of PMMA after long-term



implantation in the cranium is scant. In the literature, 1 patient was victim in a bicycle accident after cranioplasty, which resulted in a fractured PMMA cranioplasty.²² Marchac and Greensmith²³ included 32 patients who underwent a cranioplasty with PMMA,

and 1 cranioplasty was removed because of fracture because of trauma. In another study, a patient underwent a computer-based titanium mesh cranioplasty which fractured spontaneously. The authors hypothesized that the fracture of the implant occurred because of continuous pressure on the implant during the night, when the patient slept on the affected side.²⁴ Fracture is more frequently described in cranioplasties manufactured from hydroxyapatite.^{25,26} Staffa et al.²⁵ reported 25 patients who all underwent a cranioplasty of hydroxyapatite, of which 1 cranioplasty fractured because of trauma. Stefini et al.²⁶ included 1549 patients with a hydroxyapatite cranioplasty, and 4 were reported as fractured. The low incidence rate of fracture of cranioplasties could be because of underreporting of this complication in the literature. It is also possible that patients have no complaints and therefore do not notice the fracture.

The effects on molecular weight and mechanical properties for PMMA bone cements used for fixation of artificial joints are reported on in the literature. Hughes et al.²⁷ reported a 12% drop in molecular weight of Palacos (Smith & Nephew Inc., London, United Kingdom) used for fixation of the hip after 15 years in vivo. The molecular weight of Simplex (Stryker Howmedica Osteonics, Inc., Mahwah, New Jersey, USA), retrieved from hip

Table 2. Representative Gel Permeation Chromatography Results of the Implant and Reference Samples

Material	Sample Number	M_n (g/mol)	M_w (g/mol)	M_z (g/mol)	PDI
Implant	1	90,138	238,850	488,988	2.65
	2	96,789	245,156	504,793	2.53
	3	87,441	218,874	404,050	2.50
	4	87,706	241,354	487,383	2.75
CMW-3	1	88,232	234,735	471,701	2.66
	2	95,322	245,214	491,876	2.57

M_n , M_w , and M_z data are relative to polystyrene standards.

M_n , number average molecular weight; M_w , weight average molecular weight; M_z , Z average molecular weight; PDI, polydispersity index.

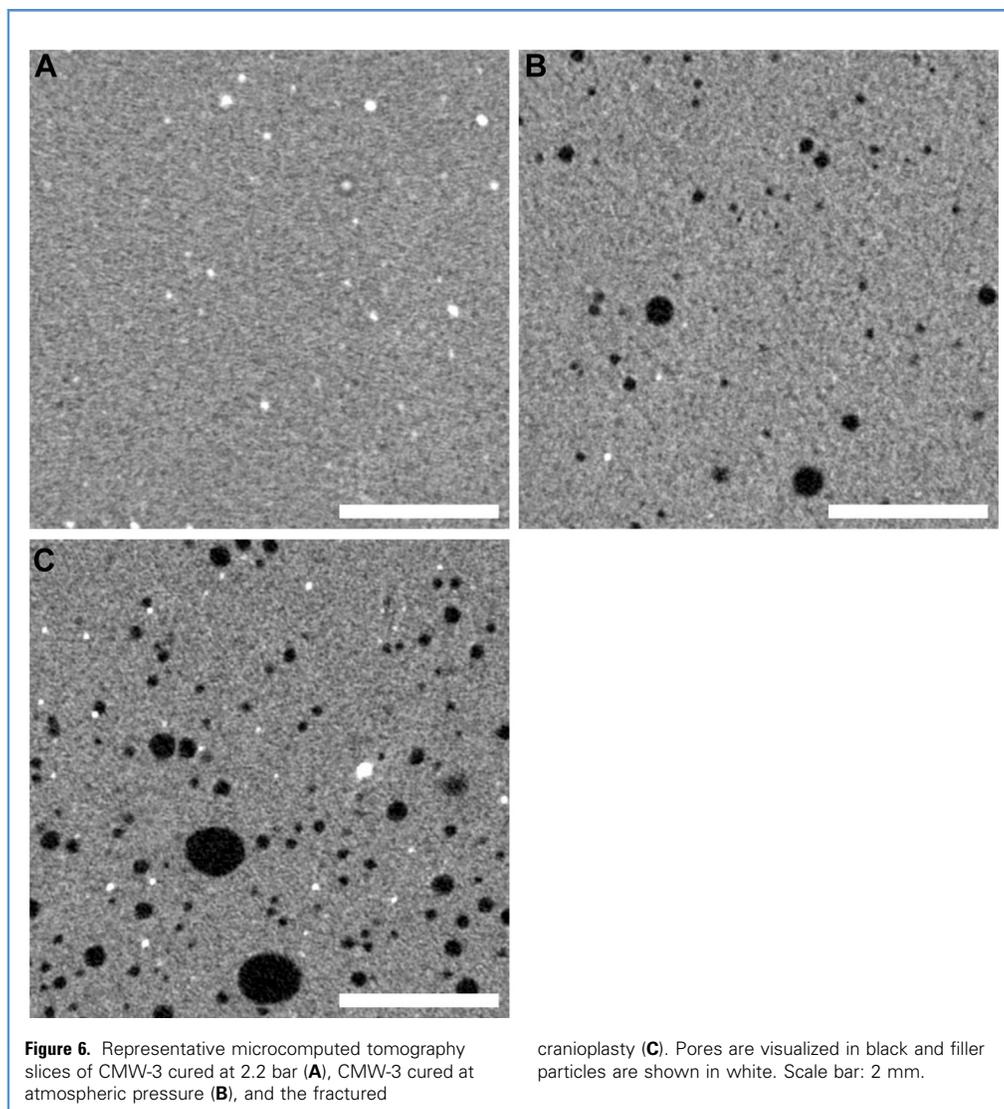


Figure 6. Representative microcomputed tomography slices of CMW-3 cured at 2.2 bar (A), CMW-3 cured at atmospheric pressure (B), and the fractured

cranioplasty (C). Pores are visualized in black and filler particles are shown in white. Scale bar: 2 mm.

fixation, was reduced by 46% after 23 years. After 16 years, no significant reduction in molecular weight was found for Simplex used for knee fixation.²⁷ CMW-1 cement, retrieved from hip fixation, was stable in vivo and did not show a reduction in molecular

weight, even after more than 20 years.²⁸ In our study, the molecular weight of CMW-3 did not significantly change during 15 years in the human cranium.

By manually manufacturing the cranioplasty during surgery, the local thickness and shape are difficult to control. The fractured PMMA cranioplasty in our study was manually manufactured and had a thickness of less than 3 mm at several locations, and point defects even up to 1.5 mm, carrying an inherent higher risk of fracture. Nowadays, this risk can be mitigated by the use of a 3D-printed nylon mold. After the mold is manufactured, it can be sterilized and used for reconstruction. During surgery, PMMA can be cured following manufacturer's instructions and put into the mold when it is moldable. Because of the mold, the PMMA can be evenly distributed with a consistent thickness, which results in fewer weak points in the implant and should therefore make it more resistant to fracture. By using a mold, the high temperatures reached during polymerization do not need to be suppressed to

Table 3. Flexural Strength (σ) of the Fractured Implant and Control Specimens

Material	Pressure	σ (MPa)
Fractured implant	Atmospheric	61.4 \pm 17.4*
CMW-3	Atmospheric	72.1 \pm 9.1*
CMW-3	2.2 bar	92.5 \pm 4.0

Values given as mean \pm SD. n = 10 per group.

*No significant difference between the groups.

Table 4. Maximum Tensile Stress (σ_{\max}) and Total Translation (l) Resulting from a Load of 100 N Perpendicular to the Top Surface of the Implant Model at the Specified Location

Location	σ_{\max} (MPa)	l (mm)
Center	3.8	0.091
Weak spot	12.2	0.159

prevent damage of the underlying tissues, leading to a final implant with a higher degree of polymerization.¹³⁻¹⁶ Preoperative ex vivo manufacturing of a PMMA cranioplasty would allow for an even better control of the environmental conditions, especially increased pressure, during polymerization, which leads to a reduced PDI and improved mechanical and biocompatibility properties. Alternative materials, especially PEEK, are increasingly being used for personalized cranioplasties using computer-aided design and computer-aided manufacturing methods because of their improved strength; however, they are significantly more expensive.⁷

Macroporosity can occur when PMMA is prepared by hand because of air getting entrapped in the material. Using a vacuum system leads to a lower macroporosity in PMMA. Similar trends are observed when reducing the speed of mixing and decreasing the number of strokes. However, when PMMA is mixed under vacuum conditions, the microporosity is increased as the boiling point of the liquid methyl methacrylate component is lowered.¹² Our study shows reduced porosity in the CMW-3 cured at atmospheric pressure with the use of a 3D-printed mold compared with the fractured implant, and a further reduction in microporosity when cured at 2.2 bar. As reported in the literature, the flexural

strength in our study is influenced by the porosity.²⁸ With increased porosity, flexural strength is reduced. The location and distribution of the pores is important because pores near the midline will experience lower stresses.

To understand why this PMMA cranioplasty fractured, FEA was performed. The FEA confirmed that the stresses increased from the center to the point defect under a load of 100 N. The load of fracture of 503 N will most probably not be reached in daily life because patients are assumed to be more vigilant and careful. However, hitting the head on a hard surface at a speed of 0.42 m/s might easily occur. The patient might not even remember such a minor incident because the patient in this case could also not recall a trauma involving the cranioplasty. The FEA model is a simplified model, modeled only with the defect at the suspected weak spot and without underlying tissues. Only the bone surrounding the implant is included. The stresses and consequently the displacements are very concentrated and of such a low level away from the weak spot that detailing of the environment is not of significant influence (Figure 7). The pressure in the head in a normal healthy human ranges from 70 to 180 mm water column.²⁹ This pressure results in an upward load distributed over the entire implant, lowering the stresses, but is hardly of influence on a concentrated load of 503 N.

These combined findings suggest that fracture of a PMMA cranioplasty is more likely to occur when features such as a reduced thickness, high porosity, and pores located near the surface are situated closely together, and an impact occurs at that specific location.

Limitations of This Study

This study included only 1 PMMA cranioplasty for analysis. To have more reliable conclusions, a larger number of fractured PMMA cranioplasties should ideally have been included. In this study, tissue formation, behavior, and changes in time have not been taken into consideration. These properties may be important and may influence failure rates in clinical circumstances; as such, they should be investigated in future studies.

CONCLUSIONS

This ex vivo study shows that a CMW-3 cranioplasty after 15 years in vivo had not resulted in a change in molecular weight or flexural strength. However, the design and manufacturing of the PMMA cranioplasty seem to be important factors for possible improvements in cranioplasties. By curing PMMA under increased pressure, the porosity is reduced. As a result, the flexural strength is increased.

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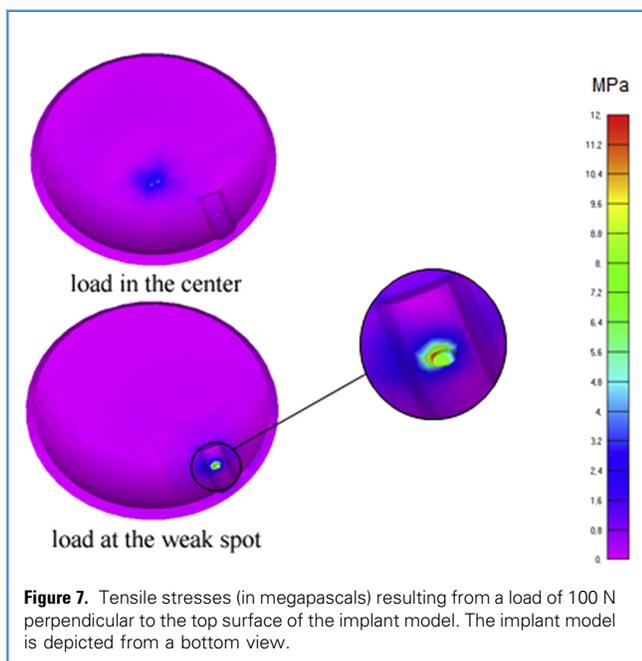


Figure 7. Tensile stresses (in megapascals) resulting from a load of 100 N perpendicular to the top surface of the implant model. The implant model is depicted from a bottom view.

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